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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/523,455	03/10/2000	Jurgen Engel	PM 264671	5040

909 7590 10/04/2004

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EXAMINER	
JIANG, SHAOJIA A	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 10/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/523,455	ENGEL ET AL.	
	Examiner	Art Unit	
	Shaojia A. Jiang	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/4/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 4, 2004 has been entered.

This Office Action is a response to Applicant's request for continued examination (RCE) filed August 4, 2004 wherein no amendment was filed with RCE. Note that the amendment has been filed May 19, 2003 which is the same amendment or the same copy of the amendment filed February 28, 2002.

Currently, claims 1 and 3-24 are pending in this application.

Claims 1 and 3-24 are examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-5, 11, and 21are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for the particular and specific LHRH-antagonists such as those recited in claims 5-9 herein, LHRH-

agonists, or LH, in combination with progestogen to be administered for the claimed method herein, does not reasonably provide enablement for any substances or compounds represented by "LHRH-antagonists", "LHRH-agonists" or LH for co-administration with progestogen.

These recitations, "LHRH-antagonists", "LHRH-agonists" or "LH", are merely functional language.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The nature of the invention: The instant invention pertains to a method of therapeutic management of infertility by programming of controlled ovarian stimulation and assisted reproductive procedures herein.

The relative skill of those in the art: The relative skill of those in the art is high.

The breadth of the claims: The instant claims are deemed very broad since these claims may reasonably encompass not only those known but also unknown "LHRH-

antagonists", "LHRH-agonists" or "LH"as of the instant filing date, even those future known "LHRH-antagonists", "LHRH-agonists" or "LH".

The amount of direction or guidance presented:

Functional language at the point of novelty, as herein employed by Applicants, is admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC, 1997) at 1406: stating this usage does "little more than outline goal appellants hope the recited invention achieves and the problems the invention will hopefully ameliorate". The CAFC further clearly states that "[A] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials" at 1405(emphasis added), and that "It does not define any structural features commonly possessed by members of the genus that distinguish from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus.." at 1406 (emphases added).

In the instant case, "LHRH-antagonists", "LHRH-agonists" or "LH", recited in the instant claims are purely functional distinction. Hence, these functional recitations read on any known or unknown or future known compounds that might have the recited functions. However, the specification merely provides those particular compounds or agnets for each kind of functional compounds in the specification.

Thus, Applicants functional language at the points of novelty fails to meet the requirements set forth under 35 U.S.C. 112, first paragraph. Claims employing functional language at the exact point of novelty, such as Applicants', neither provide those elements required to practice the inventions, nor "inform the public during the life of the patent of the limited of monopoly asserted" (*General Electric Company v. Wabash Appliance Corporation et al.* 37 USPQ at 468 (US Supreme Court 1938)).

The predictability or unpredictability: the instant claimed invention is highly *unpredictable* as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art cannot fully described genus, visualize or recognize the identity of the members of the genus, by structure, formula, or chemical name, of the claimed subject matter, as discussed above in *University of California v. Eli Lilly and Co*. Hence, in the absence of fully recognizing the identity of the members genus herein, one of skill in the art would be unable to fully predict possible physiological activities of any compounds having claimed functional properties in the pharmaceutical compositions herein.

Moreover, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutic effects, side effects, and especially serious toxicity that may be generated by drug-drug interactions when and/or after administering to a host (e.g., a

male) the ***combination*** of any compounds represented by "LHRH-antagonists", "LHRH-agonists" or "LH", and progestogen.

See text book "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions (9th ed, 1996) page 51 in particular. This book teaches that "The frequency of significant beneficial or adverse drug interactions is unknown" (see the bottom of the left column of page 51) and that "Recognition of beneficial effects and recognition of and prevention of adverse drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed" and that "The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences" (see the right column of page 51) (emphases added). In the instant case, in the absence of fully recognizing the identity of the members genus herein, one of skill in the art would not be able to fully predict possible adverse drug-drug interactions occurring with many combinations of any compounds having claimed functional properties in the pharmaceutical compositions herein to be administered to a host. Thus, the teachings of the book clearly support that the instant claimed invention is highly unpredictable.

Further, these recitations may broadly encompass those known and **unknown** compounds having the recited functions as of the instant filing date, as discussed above. These recitations broadly encompass those known and **unknown** compounds having the recited functions as of the instant filing date. Note those **future known** compounds yet to be discovered and/or made. Hence, those unknown or future known

compounds encompassed by claim 1 herein must require to additional or future research to discover, establish or verify their usefulness. Therefore, as indicated in the previous Office Action, the skilled artisan has to exercise **undue experimentation** to practice the instant invention.

The presence or absence of working examples and the quantity of experimentation necessary:

As discussed above, only those particular compounds for each kind of functional compounds employed in the composition herein is disclosed in the specification. Moreover, it is noted that only an example by testing a single particular combination is disclosed in the specification (see page 5-6 of the specification). Thus, the evidence in the examples is also not commensurate in scope with the claimed invention and does not demonstrate criticality of a claimed range of the active agents or compounds in the claimed composition. See MPEP § 716.02(d).

Since any significant structural variation to a compound would be reasonably expected to alter its properties, one of ordinary skill would be required to perform undue experimentation to determine which, if any compounds represented by "LHRH-antagonists", "LHRH-agonists" or "LH", and progestogen would be useful in the claimed particular treatment.

Thus, the specification fails to provide clear and convincing evidence in sufficient support of the broad use of any compounds having those functions recited in the instant claims. As a result, necessitating one of skill to perform an exhaustive search for the

embodiments of any known and unknown compounds having those functions encompassed in the instant claims suitable to practice the claimed invention.

Genentech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors, the case *University of California v. Eli Lilly and Co.* (CAFC, 1997) and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in *undue experimentation* to test all compounds encompassed in the instant claims and their combinations to be administered to a woman in the claimed method of the treatment, with no assurance of success.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 3-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Engel et al. (EP 0788 799, of record) and Albano et al. (of record) and Felberbaum et al. (of record) and Garfield (5,470,847, of record) in view of Deghenghi (5,945,128, of

record) and Rabasseda et al. (of record) and Kent (4,016,259 of record) for reasons of record stated in the Office Action dated October 1, 2003.

Engel et al. discloses that an LHRH-antagonist, such as cetrorelix, is useful in the method of suppression of premature ovulation in controlled ovarian sitmulation and assisted reproductive techniques, e.g., ICSI or intrauterine insemination by sperm injection, with multiple follicle and oocyte development. See the abstract, col. 1 lines 10-20, 30-34, 39-59, col. 2 lines 1-13, 16-25, col.3 lines 1-12, and claims 1-14. Engel et al. also discloses exogeneous stimulation of the ovarian follicle growth and ovulation induction with HCG, LHRH, or LHRH-agonists and the stimulation is performed by administration of FSH or HMG with or without recombinant LH. See Abstract, col. 2 lines 38-43. Engel et al. further discloses the effective amount of the LHRH-antagonist cetrorelix within the instant claim to be administered during luteal phase. See Examples claim 6-8. Finally, Engel et al. teaches progesterone is useful in supporting the beginning of pregnancy. See col.1 lines 23-24.

Albano et al. teaches that LHRH-antagonists, such as cetrorelix, are useful in the method of suppression of premature ovulation in controlled ovarian sitmulation and assisted reproductive techniques, e.g., IVF and ICSI, with multiple follicle and oocyte development, as well as the effective amount of the LHRH-antagonist cetrorelix within the instant claim to be administered during luteal phase. See Abstract, Introduction and Results. Albano et al. further teaches that progesterone concentration is significantly lowered due to the administration of cetrorelix. See page 2115, 5th paragraph of right column.

Felberbaum et al. teaches that LHRH-antagonists, such as cetrorelix and ganirelix, are useful in the method of suppression of premature ovulation in controlled ovarian sitmulation and assisted reproductive techniques, e.g., IVF and ICSI, with multiple follicle and oocyte development, as well as the effective amount of the LHRH-antagonist cetrorelix within the instant claim to be administered during luteal phase. See Abstract, page 399-402 Felberbaum et al. further teaches a fall of sex steroids due to the administration of LHRH-antagonists. See page 398, the last three lines.

Garfield teaches that the administration of progestogen in the follicular phase is useful along with other progestins, an estrogen, e.g. ethinylestradiol, and an LHRH-antagonist in a method of controlling ovarian stimulation and preventing conception. See abstract, col.1 lines 18-67 and col.5 lines 35-38. Garfield also teaches that the ovarian stimulation is achieved with antioestrogens, such as clomiphene, combined with gonadotropins. See col. 2 lines 9-17, col.5 lines 64-67 and col.6 lines 30-40.

The prior art does not expressly disclose that the particular LHRH-antagonist are teverelix, antide, and abarelix and their effective amounts to be administered. The prior art does also not expressly disclose that the ovarian stimulation therapy may be on Fridays to Mondays, and ooctye pick up and ART may be undertaken on Mondays to Thursdays. The prior art does not expressly further disclose the particular employment of oral contraceptive preparations containing progestogen and mestranol in the management of infertility.

Deghenghi discloses cetrorelix, teverelix, ganirelix and antide are known to be LHRH-antagonists. see col.2 lines 19-23.

Rabasseda et al. teach that LHRH-antagonists such as cetrorelix, ganirelix, and abarelix are known to be useful in the treatment of female infertility (see Introduction and Table 1 of page 397).

Kent discloses that the combination of progestogens and estrogen, i.e., mestranol and ethinylestradiol is useful in animal contraception (see col.1 lines 20-25).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ the particular LHRH-antagonist such as teverelix, antide, and abarelix and to optimize their effective amounts to be administered, and to schedule or program the ovarian stimulation therapy on Fridays to Mondays and ooctye pick up and ART on Mondays to Thursdays, to employ the particular estrogen, mestranol, in oral contraceptive preparations along with progestogen.

One having ordinary skill in the art would have been motivated to employ the particular LHRH-antagonist such as teverelix, antide, and abarelix since teverelix, antide, and abarelix are known to be LHRH-antagonists, useful in the methods of controlled ovarian situmlation and assisted reproductive techniques and of the treatment of infertility according to Engel et al., Albano et al., Felberbaum et al., Deghenghi and Rabasseda et al. Additionally, one of ordinary skill in the art would have been motivated to optimize the effective amounts of active ingredients in the composition because the optimization of amounts of active agents to be administered is considered well within the skill of artisan. One having ordinary skill in the art would have been motivated to schedule or program the ovarian stimulation therapy on Fridays to Mondays and ooctye pick up and ART on Mondays to Thursdays since scheduling or programming the

known ovarian stimulation therapy for Fridays to Mondays according to the calendar is considered well within the skill of artisan as the optimization of a result effective parameter, e.g., dosage regimen. One having ordinary skill in the art would have been further motivated to employ the particular estrogen, mestranol, in oral contraceptive preparations along with progestogen in the management of infertility since the known contraceptive preparations of Kent contain mestranol and progestogen, and estrogen and progestin containing contraceptive agents are known broadly to be useful in the therapeutic management of infertility.

Since all method and composition components herein are known to be useful to treat or manage the infertility, it is considered prima facie obvious to combine them into a single method useful for the very same purpose. See *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980).

Applicant's remarks filed on May 19, 2003 in Paper No. 17 with respect to this rejection of claims 1 and 3-24 made under 35 U.S.C. 103(a) have been fully considered but are not deemed persuasive as to the nonobviousness of the claimed invention over the prior art for the following reasons.

Again, Applicant's arguments that the cited references, either alone or in combination does not render the presently claimed invention unpatentable have been considered but are not found persuasive.

Applicant asserts the citation of seven different and unrelated documents. Contrary to Applicant's assertion, all cited references, especially all primary references,

Engel et al., Albano et al., Felberbaum et al. and Garfield, clearly disclose the methods of suppression of premature ovulation in controlled ovarian sitmulation and assisted reproductive techniques.

As discussed in the previously Office Action, the instant LHRH-antagonists such as teverelix, antide, and abarelix are known to be LHRH-antagonists and known to be useful in the methods of controlled ovarian situmlation and assisted reproductive techniques and of the treatment of infertility according to Engel et al., Albano et al., Felberbaum et al., Deghenghi and Rabasseda et al. Thus, each step in the instant claimed method is known in the prior art. It must be recognized that any judgment on obviousness takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made. See MPEP 2145.

Further, the particular estrogen herein, mestranol, in oral contraceptive preparations in combination with progestogen are well known contraceptive agents and also known broadly to be useful in the therapeutic management of infertility according to the prior art. Therefore, one of ordinary skill in the art would have reasonably expected that combining these particular agents known useful for the same purpose in a composition to be administered would produce additive therapeutic effects to improve the treatment of in the therapeutic management of infertility, absent evidence to the contrary.

Since all active composition components herein are known to useful in the therapeutic management of infertility, it is considered prima facie obvious to combine them into a single composition to form a third composition useful for the very same

purpose. At least additive therapeutic effects would have been reasonably expected based on the well settled principle set forth *In re Kerkhoven* regarding combination inventions. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller, 642 F.2d 413, 208 SPQ 871 (CCPA 1981); In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). See MPEP 2145.

Therefore, motivation to combine the teachings of the prior art cited herein to make the present invention is seen. The claimed invention is clearly obvious in view of the prior art.

Applicant's results of the instant method (program) in the specification at page 4-5 herein have been fully considered with respect to the nonobviousness and/or unexpected results of the claimed invention over the prior art but are not deemed persuasive for the reasons below. The results provide no clear and convincing evidence of nonobviousness or unexpected results over the cited prior art since there is no side-by-side comparison with the closest prior art. Therefore, the evidence presented in specification herein is not seen to support the nonobviousness of the instant claimed invention over the prior art.

For the above stated reasons, said claims are properly rejected under 35 U.S.C. 103(a). Therefore, said rejection is adhered to.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 and 3-24 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,319,192.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent is drawn to a method of therapeutic management of infertility by intrauterine insemination consisting of substantially similar method steps and administering the same pharmaceutical agents, i.e. an LHRRH-antagonist such as cetrorelix, HCG, native LHRH, LHRH-agonists or recombinant LH.

The claims of the instant application is drawn to the method of therapeutic management of infertility by programming of controlled ovarian stimulation and assisted reproductive procedures the improvement.

One having ordinary skill in the art would clearly recognize that the method in the patent and the method in the instant application consisting of substantially similar method steps and administering the same pharmaceutical agents are seen to substantially overlap.

Thus, the instant claims 1 and 3-24 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,319,192.

In view of the rejections to the pending claims set forth above, no claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (571)272-0627. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703.872.9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

S. Anna Jiang, Ph.D.
Primary Examiner, AU 1617
September 28, 2004